# COMBINATION THERAPY FOR LOWER URINARY TRACT SYMPTOMS

## Field of the Invention

This invention relates to combination therapy for the treatment of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS), whether or not associated with BPH. The combination therapy comprises the use of $\alpha_{1a}$ adrenergic receptor (AR) subtype selective antagonists in combination with muscarinic receptor antagonists and optionally including 5$\alpha$-reductase inhibitors, for relief of LUTS in a subject, with or without BPH.

## Background of the Invention

Benign prostatic hyperplasia (BPH) also known as benign prostatic hypertrophy is highly prevalent in men beyond the age of 50 and increases in severity and incidence with increasing age. The incidence is 70% in 70 years and becomes nearly universal with advancing age with 90% incidence at the age of 80 years [Berry et al., *J. Urol.* 132: 474-479 (1984)].

Symptomatic BPH is thought to be due to bladder outflow obstruction and is usually suggestive of the lower urinary tract symptoms [Speakman, *Eur. Urol. Suppl.* 40, 21, (2001)]. BPH is characterized by nodular enlargement of prostatic tissue and is associated with variety of lower urinary tract symptoms (LUTS). LUTS in men includes, but is not, restricted to a complex of obstructive (voiding) and irritative (storage or filling) symptoms which include increased frequency, nocturia, a poor urinary stream and hesitancy or delay in starting urinary flow. Chronic consequences of BPH can include hypertrophy of bladder smooth muscle, a decompensated bladder and increased incidence of urinary tract infections. Histologically, BPH is characterized by glandular (epithelial) and stromal (fibromuscular) hyperplasia with the latter being the dominant factor in the pathogenesis of clinically significant BPH [Shapiro *et al*, J Urol 147: 1293-1297 (1992)].

Though the exact etiology of origin of these symptoms is not distinctly clear, two components, a static component and a dynamic component, clearly contribute to obstruction. Prostatic enlargement or hyperplasia of prostate gland physically impinges on the free flow of fluids through the male urethra and leads to varying degrees of bladder obstruction. This component has been referred to as the static component [Caine M, *J.*

*Urol.* 136: 1-4 (1986)]. Increased adrenergic innervation to prostate leads to an increased adrenergic tone of the bladder neck or urethra and is referred to as dynamic component. The irritative symptoms have been closely associated with bladder dysfunction which was believed to be a consequence of bladder outlet obstruction [Anderson K. E., *Brit. J. Urol.* 85 Suppl: 12-18 (2000)].

Standard treatments for BPH involve surgical or pharmacological intervention. Surgical intervention involves removal of the prostate via radical prostectomy or removing the prostate adenoma via transurethral resection of the prostate. These invasive surgical procedures have limited utility because of the morbidity associated with operative procedures as well as the persistence and recurrence of obstructive and irritative symptoms. Surgical procedures are, therefore, not recommended for patients exhibiting mild to moderate symptoms.

Presently, pharmacological interventions in the treatment of BPH can be distinctly categorized into two main categories: - α1 AR antagonists and testosterone 5α-reductase inhibitors. Testosterone 5α reductase inhibitors such as finasteride and dutasteride reduce the size of prostate [Wilde et al., *Drugs* 57: 557-581 (1999)], thereby alleviating the static component of bladder outlet obstruction. The lesser efficacy associated with these inhibitors is mechanism-based, in that testosterone 5α-reductase inhibitors decrease the size of prostate by reducing the amount of epithelial tissue without affecting the smooth muscle and the dynamic component of bladder outlet obstruction.

Other pharmacological therapy involves the administration of subtype non-selective α1 AR antagonists. These agents relax prostatic-urethral smooth muscle by blocking the α1 mediated effects on endogenous tone hence affecting the dynamic component of bladder outlet obstruction and relieving obstructive symptoms [Chapple, *Brit. J. Urol.* 1: 47-55 (1995), Kawabe and Niijima, *Urol. Int.* 42: 280-284 (1987), Lepor et al, *J. Urol.* 148: 1467-1474 (1992), Reuther and Aagard, *Urol. Int.* 39: 312-313 (1984), Serels and Stein, *Neurourol. Urodyn.* 17: 31-36 (1998)]. In addition these α1 AR antagonists have also been found to relieve the irritative bladder symptoms associated with BPH.

Alpha adrenoceptors are members of a larger G protein-coupled adrenergic receptors family, which mediates the actions of endogenous catecholamines norepinephrine and epinephrine resulting in smooth muscle contraction. cDNA's encoding

three distinct α1 AR subtype ($\alpha_{1a}$, $\alpha_{1b}$ and $\alpha_{1d}$) and three distinct α2 adrenoceptor subtypes ($\alpha_{2a}$, $\alpha_{2b}$ and $\alpha_{2c}$) have been cloned, expressed stably in cells and resultant protein characterized pharmacologically [Schwinn et al, *J. Pharmacol. Exper. Ther.* 272: 134-142 (1995), Hieble et al., *Pharmacol. Rev.* 47: 267-70 (1995)].

Human lower urinary tract contains both α1 and α2 AR, with the latter predominating the former [Goepel et al., *Urol. Res.* 25:199-206 (1997)]. However the prostatic smooth muscle contraction is mediated predominantly, if not exclusively by α1-AR [Hieble et al., *Eur. Pharmacol.* 107: 111-117(1985), Chappel et al., *Brit. J. Urol.* 63; 487-496 (1989)].

α1 ARs predominate in prostate and bladder trigone [Price et al., *J. Urol.* 150: 546-551 (1993)], and have been shown to be functionally important in mediating smooth muscle contraction [Forray et al., *Mol. Pharmacol.* 45: 703-708 (1994), Lepor et al., *J. Pharmacol. Exper. Ther.* 270:722-727 (1994)]. In addition to the three-cloned α1 AR subtypes which have high affinity for the prazosin a fourth type of $\alpha_1$ AR with low affinity for prazosin ($\alpha_{1L}$) has been postulated [Muramatsu et al., *Brit. J. Urol.* 74: 572-578 (1994)]. However, there is evidence to suggest that it may represent functional phenotype of the α1AR [Daniels D.V., *Eur. J. Pharmacol.* 370: 337-43(1990)].

The non-subtype selective α1 AR antagonists such as prazosin, terazosin and doxazosin and alfuzosin are accompanied by side effects such as postural hypotension, dizziness and syncope. These side effects are attributed to the affinity towards non-selective α1 AR subtypes in the vasculature [*J. Androl.* 18: 345-355 (1991)]. Therefore, in an attempt to develop α1 AR antagonist with minimal cardiovascular effect, the concept of developing $\alpha_{1a}$ subtype selective antagonists with minimal affinity for $\alpha_{1b}$ and $\alpha_{1d}$ subtype in BPH was proposed which is extensively covered in United States Patent Nos. 5,403,847; 5,578,611; 5,780,485; 5,990,128; and 6,015,819.

Development of several $\alpha_{1a}$ subtype selective compounds with minimal affinity for $\alpha_{1b}$ and/or $\alpha_{1d}$ AR has been reported. The selective $\alpha_{1a}$ AR antagonists cause significantly smaller blood pressure alterations and fewer cases of orthostatic hypertension, as compared to nonselective α1 AR antagonists [Michael M. C., *Eur. Urol. Supp.* 5-13 (2002)].

Recent studies, however suggest that the relief of bladder outlet obstruction only partly explain involvement of lower urinary tract with these agents. There is poor correlation in BPH patients between obstructive (voiding) and irritative (storage) symptoms and urine flow rates at base line. The irritative symptoms can persist despite the relief of bladder outlet obstruction [Hieble and Ruffolo, Jr., *Exp. Opin. Invest. Drug* 6: 367-387 (1997)].

In recent clinical studies with experimental antagonists with high affinity for $\alpha_{1a}$ ARs and particularly devoid of $\alpha_{1d}$ activity have demonstrated enhancements in the urine flow rates without any improvement on irritative LUTS [Blue et al., *J. Urol.* 167 (Suppl) 265 (2002)].

Irritative symptoms such as urgency and frequency traditionally associated with BPH is also observed in LUTS in women suffering from detrusor instability suggesting thereby these symptoms are caused by similar mechanisms or are amenable to a single form of therapy [Staskin, D. R. et al., *Urology* 60 (Suppl 5A) (2002) 1-6].

The two main functions of the urinary bladder are to store urine and to empty it, by involving a complex pattern of nerve signalling. Disturbances in the normal control of the bladder reflexes may lead to an "overactive bladder", clinically characterized by symptoms of urgency, frequency, nocturia and urge incontinence. Bladder excitability is under the control of parasympathetic nervous system and releases the neurotransmitter acetylcholine. Acetylcholine acts on protein recognition sites in bladder known as muscarinic receptors.

Muscarinic receptors are G-protein coupled receptors, encoded by five distinct genes [Caulfield and Birdsall, *Pharmacol. Rev.* 50: 279-290 (1998)]. These characterize five distinct molecular and pharmacological subtypes namely M1, M2, M3, M4 and M5. Normal human bladder contraction is mediated mainly through stimulation of muscarinic receptors in detrusor muscle by the endogenous ligand, acetycholine. The muscarinic receptors found in human detrusor are of M2 and M3 subtypes [Hedge and Eglen, *Life Sci.* 64: 419-428 (1999), Fetscher et al., *Brit. Jr. Pharmacol.* 136: 641-644 (2002)]. M2 receptors predominate in number over M3 subtype but it is M3 receptors, which are mainly responsible for the normal micturition contraction [Yamanishi et al., *World J. Urol.* 19: 299-306 (2001)]. Muscarinic receptors are involved in both normal and disturbed bladder contraction, and therefore the most common drug treatment of

overactive bladder are muscarinic receptor antagonists also referred to as antimuscarinic drugs. Antimuscarinics block more or less selectively muscarinic receptors on the bladder smooth muscles (detrusor), which are stimulated by acetylcholine. Thereby they decrease the ability of bladder to contract. Antimuscarinic drugs act mainly during the storage phase, increase the bladder capacity and decrease the urge.

In the patients of outflow obstruction, as in BPH, muscarinic receptor antagonists have generally been contraindicated for symptomatic relief because of the possible risk of urinary retention [Sullvian et al., *Eur. Urol.* 36 (Suppl 1), 89-95 (1999)]. A number of reports of urinary outflow obstruction induced in patients given ipratropium by aerosol for respiratory conditions have been recorded by Lozewicz [Lozewicz, S., *Postgrad Med. J.* 65: 260-261 (1989)]. These patients were found to have enlarged prostate gland.

Recently, administration of tolterodine, a antimuscarinic drug in men with bladder outlet obstruction and symptomatic detrusor overactivity was not associated with any safety concerns [Abrams, P. et al., *Eur. Urol.* 1: 132 (2002) (abstract 520)]. A combination therapy for the treatment of BPH comprising $\alpha_{1a}$ AR antagonist and an endothelin antagonist has been disclosed in U.S. Patent No. 6,410,554. A combination of a dyphylline-type compound with $\alpha$ AR antagonist and/or 5$\alpha$- reductase inhibitor for the treatment of BPH has been disclosed in U.S. Patent No. 6,423,719. WO 99/57131 discloses a method of identifying $\alpha_{1d}$ AR antagonists that can be used to treat irritative symptoms of BPH. A combination of $\alpha_{1a}$ AR antagonist with 5$\alpha$-reductase inhibitor for the treatment of BPH has been disclosed in U.S. Patent No. 6,376,503. A method of treating LUTS and pharmaceutical composition comprising a muscarinic receptor antagonist and at least one other active ingredient selected from a 5$\alpha$-reductase inhibitor and an $\alpha$ AR antagonist have been disclosed in WO 01/21167. Pharmaceutical combinations comprising $\alpha$ AR antagonist and a muscarinic receptor antagonist for the treatments of LUTS associated with BPH in men are disclosed in U.S. Patent Application No. 2001/0044438.

Combinations of selective $\alpha_{1a}$ subtype adrenoceptor antagonists with muscarinic receptor antagonists are not previously known, therefore, patients are prone to side effects (such as hypotension) associated with non-selective $\alpha$1 AR antagonist.

## Summary of the Invention

Herein is provided a combination of a selective $\alpha_{1a}$ AR antagonists, muscarinic receptor antagonists, and optionally included testosterone 5α-reductase inhibitors for use as a medicament for the treatment of BPH and LUTS, whether or not associated with BPH.

The pharmaceutical compositions provided herein can comprise a combined preparation of a first pharmaceutically acceptable composition comprising a selective $\alpha_{1a}$ AR antagonist, a second composition comprising a muscarinic receptor antagonist, and an optionally included third pharmaceutically acceptable composition comprising a 5α-reductase inhibitor. The combined preparation may be used simultaneously, separately or sequentially.

Further provided herein is a pharmaceutical composition comprising a selective $\alpha_{1a}$ AR antagonist, a muscarinic receptor antagonist and, optionally included, a testosterone 5α-reductase inhibitor and a pharmaceutically acceptable carrier for the treatment of BPH and LUTS, whether or not associated with BPH.

Methods for the treatment of BPH and LUTS in a mammal are also provided comprising administering to mammal in need thereof an effective amount of a selective $\alpha_{1a}$ AR antagonist in combination with a muscarinic receptor antagonist and optionally included testosterone 5α-reductase inhibitor. The combination may be administered simultaneously, separately or sequentially.

The combination of $\alpha_{1a}$ selective antagonist and muscarinic selective antagonists offers advantages of relieving LUTS more effectively in patients with BPH and obstructive symptoms, with minimal side effects such as fall in blood pressure. This combination will also be useful in obstructive LUTS in women and treatment of LUTS in men in absence of BPH.

## Detailed Description of the Invention

Along with the individual components of the composition, their pharmaceutically acceptable salts are also included. The pharmaceutically acceptable salts include, for example, alkali metal salts and addition salts of acids or bases. Suitable pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Example of such inorganic acids include, but are not limited to, hydrochloric,

hydrobromic, hydroiodic, nitrous (nitrite salt), nitric (nitrate salt), carbonic, sulfuric, phosphoric acid and like. Appropriate organic acids include, but are not limited to, aliphatic, cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids such as, for example, formic, acetic, propionic, succenic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumeric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, algenic, beta-hydroxybutyric, cyclohexylaminosulfonic, galactaric and galacturonic acid and the like. Suitable pharmaceutically acceptable base addition salts include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, and procaine and the like. The salt forms can differ from the compounds described herein in certain physical properties, such as solubility in polar solvent, but the salts generally retain the physiological utility of the non-salt compounds.

Prodrugs of these pharmaceutical agents are also provided herein. In general, such prodrugs will be functional derivatives of these compounds, which are readily convertible *in vivo* into the required compound. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed.H Bundgaard et al. and, Elsevier, 1985. Metabolites, which become active upon introduction into the biological system, are also included herein. Where the compounds described herein have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds described herein possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures therefore are provided in this disclosure. Furthermore, some of the crystalline forms for compounds described herein may exist as polymorphs and as such are included in the present disclosure. In addition, some of the compounds described herein may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also provided herein.

The term "selective" as used in "selective $\alpha_{1a}$ AR antagonist" refers to those agents, which are more than about ten fold selective for $\alpha_{1a}$ AR as compared to $\alpha_{1b}$ and/or

$\alpha_{1d}$ ARs in receptor binding assay or *in vitro* functional assay. Particular selective $\alpha_{1a}$ AR antagonists can be, for example:

-5,6-Dihydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]propyl}-hexahydro-isoindole-1,3-dione and its pharmaceutically acceptable salts,

-1-{3-[4-(2-isopropoxyphenyl)piperazin-1-yl]propyl}-piperidine-2,6-dione and its pharmaceutically acceptable salts,

-2-{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}-3a,4,7,7a-tetrahydro-isoindole-1,3-dione and its pharmaceutically acceptable salts,

-1-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)piperidine-2,6-dione and its pharmaceutically acceptable salts,

-5-Hydroxy-2-(3-{4-[2-(2,2,2-trifluoroethoxyphenyl]-piperazin-1-yl}propyl)-hexahydro-isoindole-1,3-dione and its pharmaceutically acceptable salts,

-2-{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}-5-hydroxy-hexahydro-isoindole-1,3-dione and its pharmaceutically acceptable salts,

-2-{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}-5,6-dihydroxy-isoindole-1,3-dione and its pharmaceutically acceptable salts,

-4,7-Dihydroxy-2-{3-[4-(2-isopropoxyphenyl)-piperazin-1-yl]propyl}-hexahydro-isoindole-1,3-dione and its pharmaceutically acceptable salts,

-3-Allyl-1-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl}-4-methyl-pyrrolidine-2,5-dione and its pharmaceutically acceptable salts, and

-1-(2-Hydroxy-3-{4-[2-(2,2,3,3,3-pentafluoropropoxy)phenyl]-piperazin-1-yl}propyl)-piperidine-2,6-dione and its pharmaceutically acceptable salts.

The muscarinic receptor antagonists (MRAs) may be widely chosen from among those already known to the prior art or subsequently discovered and/or hereafter discovered and/or hereafter developed. MRAs have been described in United States Patent Nos. 5,096,890 and 5,233,053; EP 388054, EP 325571, EP 801067, GB 940540, and WO 98/05641. Particular MRSs can be, for example:

-(R)-2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl-phenol (tolterodine) and its pharmaceutically acceptable salts,

-(S)-alpha-cyclohexyl-alpha-hydroxybenzaeneacetic acid-4-(diethylamino)-2-butynyl ester (oxybutynin) and its pharmaceutically acceptable salts,

-(S)-1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]alpha,alpha-diphenyl-3-pyrrolidine acetamide (darifenacin) and its pharmaceutically acceptable salts,

-(1S)-(3R)-1-azabicyclo[2,2,2]oct-3-yl-3,4-dihydro-1-phenyl-2(1H)-isoquinolinecarboxylate (solifenacin) and its pharmaceutically acceptable salts,

-2-[(1R)-3-(diisopropylamine)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate and its pharmaceutically acceptable (fesoterodine),

-2-Methyl-α,α-diphenyl-1H-imidazole and its pharmaceutically acceptable salts (KRP197),

-(2R)(+)(1α, 5α, 6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenylacetamide and its pharmaceutically acceptable salts,

-(2R, 2S) (1α, 5α, 6α)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenylacetamide and its pharmaceutically acceptable salts,

-(2R) (1α, 5α, 6α)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenylacetamide and its pharmaceutically acceptable salts,

-(2S) (1α, 5α, 6α)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenylacetamide and its pharmaceutically acceptable salts.

Testosterone 5α-reductase inhibitors may be widely chosen from among those already known to the prior art or subsequently discovered and/or hereafter discovered and/or hereafter developed. The compounds that are inhibitor of testosterone 5α-reductase inhibitor have been disclosed in United States Patent Nos. 5,595,985; 4,377,584; 4,760,071; 5,017,568; 5,155,107; and 5,565,467; EP 0572165, WO 93/23420, EP 0572166, WO 93/23050, WO 93/23038, WO 93/23048, WO 93/23041, WO 93/23040, WO 93/23039, WO93/23376, WO 93/23419, and WO 93/23051. Compounds may be

inhibitor of a type 1 or type 2 testosterone 5α-reductase isoenzymes or both a type 1 and type 2 or a dual type 1 and type 2, preferably a dual type 1 and type 2 or a type 2 inhibitor, these compounds can be, for example, finasteride, dutasteride, epristeride or turosteride.

There are provided products or medicaments comprising a pharmaceutically acceptable composition containing a therapeutically effective amount of a selective $\alpha_{1a}$ AR antagonist disclosed herein and a second pharmaceutically acceptable composition containing therapeutically effective amount of a muscarinic receptor antagonist and optionally included therapeutically effective amount of testosterone 5α-reductase inhibitor as a combined preparation for simultaneous, separate or sequential administration for the treatment of BPH and LUTS with or without BPH. LUTS may include, for example, obstructive symptoms such as hesitancy, poor stream, prolong urination, and feelings of incomplete emptying, and irritative symptoms such as frequency, urgency, nocturia and unstable bladder contractions. The term "therapeutically effective amount," as used herein, means that amount of active compound that elicits the biological or medicinal response in a mammal which provides at least partial alleviation of some symptoms of the disease being treated.

There are also provided pharmaceutical compositions containing a therapeutically effective amount of a selective $\alpha_{1a}$ AR antagonist disclosed herein, a therapeutically effective amount of a muscarinic receptor antagonist and optionally a therapeutically effective amount of testosterone 5α-reductase inhibitor for the treatment of BPH and LUTS with or without BPH.

There are also provided pharmaceutical compositions containing selective alpha 1a AR antagonist as disclosed herein, a MR antagonist and optionally a testosterone 5-alpha reductase inhibitor in combination with pharmaceutically acceptable carriers, diluents or excipients.

The compositions described herein include both those containing only one component and those containing selective $\alpha_{1a}$ AR, muscarinic receptor antagonist and optionally included testosterone 5α-reductase inhibitor, which may be suitable for oral, parenteral, topical, transdermal, cholonic or intravaginal administration. The composition may be formulated to provide immediate or sustained release of the therapeutic agents. The agents described herein can be administered alone but will generally be administered as an admixture with a suitable "pharmaceutically acceptable carrier". The term

"pharmaceutically acceptable carrier" is intended to include non-toxic, inert solid, semi-solid or liquid filter, diluent, encapsulating material or formulation auxiliary of any type.

Solid form preparations for oral administration may include capsules, tablets, pills, powders, granules and suppositories. For solid form preparations, an active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate, dicalcium phosphate and/or a filter an extender such as starch, lactose, sucrose, glucose, mannitol and silicic acid; binders such as carboxymethyl cellulose, alginates, gelatins, polyvinylpyrrolidinone, sucrose, acacia; disintegrating agents such as agar-agar, calcium carbonate, potato starch, aliginic acid, certain silicates and sodium carbonate; absorption accelators such as quaternary ammonium compounds; wetting agents such as cetyl alcohol, glycerol, monostearate; adsorbents such as kaolin; lubricants such as talc, calcium stearate, magnesium stearate, solid polyethyleneglycol, sodium lauryl sulphate and mixture thereof.

In case of capsules, tablets, or pills, the dosage form may also comprise buffering agents. Solid preparations of tablets, capsules, pills, granules can be prepared with coating and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art.

Liquid form preparations for oral administration can include pharmaceutically acceptable emulsions, solution, suspensions, syrups and elixirs. For liquid form preparations, an active compound is mixed with water or other solvent, solubilizing agents and emulsifiers such as ethylalcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (such as cottonseed, groundnut, corn, germ, olive, castor and sesame oil), glycerol and fatty acid ester of sorbitan and mixture thereof.

Besides inert diluents, oral compositions can also include adjuvants such as wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents and perfuming agent.

Injectable preparations such as sterile injections, aqueous or oleaginous suspensions may be formulated according to the art using suitable dispersing or wetting and suspending agents. Among the acceptable vehicles and solvents that may be employed are water, Ringers solution and isotonic sodium chloride.

Dosage forms for topical or transdermal administration include ointments, pastes, creams, lotions, gel, powders, solutions, spray, inhalants or patches. The active compound

is admixed under sterile condition with a pharmaceutically acceptable carrier and any needed preservatives or buffer as may be required.

The pharmaceutical preparation can be prepared in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component.

The formulations as described herein may be formulated so as to provide quick sustained, or delayed release of the active ingredients after administration to the patient by employing procedures well known to the art. The compositions may be administered as a depot formulation that permits sustained release, limits access to general circulation, and increases the prostate and/or bladder-specific localization of the composition. Such a formulation may be provided as a slow release implant, be microencapsulated, or attached to a biodegradable polymers or a prostate-specific immunoglobulin. The compound is administered in a sustained release formulation as a tablet or capsule. A sustained release formulation is a preparation that releases the active component over a desired period of time after administration. A sustained release formulation is prepared by applying a biodegradable, bioerodible or bioabsorbable polymeric formulation that is compatible on the surface of the active component. Examples of sustained release formulations include, but are not limited to, hydroxypropylmethylcellulose (HPMC), hydrogenated vegetable oil (HVO), ethylcellulose, polyvinylpyrrolidione, pyran copolymer, polyhydroxypropylmethacryl – amidephenol, polyhydroxy – ethylaspartamidephenol, or polyethyleneoxidepolylysin substituted with palmitoyl residues, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydro-pyrans, or polycyano acrylates.

The term "biodegradable" means that the polymeric formulation degrades over time by the action of enzymes, by hydrolytic action and/or by other similar mechanisms in the human body. By "bioerodible" it is meant that the polymeric formulation erodes or degrades over time due, at least in part, to contact with substances found in the surrounding tissue fluids or cellular action. By "bioabsorbable", it is meant that the polymeric formulation is broken down and absorbed within the body of a mammal, for example, by a cell or tissue. "Biocompatible" means that the polymeric formulation does not cause substantial tissue irritation or necrosis.

The compounds described herein can also be administered in the form of liposome delivery systems, for example, small unilamellar vesicles, large unilamellar vesicles and

multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, for example, cholesterol, stearylamine or phosphatidylcholines.

Aqueous parenteral compositions, may contain a therapeutically effective amount of selective alpha 1a AR antagonists disclosed herein, muscarinic receptor antagonist and optionally included 5-alpha reductase inhibitor. The invention also provides a method of delivery such that direct intraprostatic injection of therapeutically effective amount of disclosed compositions result in the relieve of the obstructive symptoms associated with benign prostatic hyperplasia.

Methods of treating BPH and LUTS with or without BPH are also provided comprising the administration of a therapeutically effective amount of selective $\alpha_{1a}$ AR antagonist, therapeutically effective amount of a muscarinic receptor antagonist and optionally included testosterone 5α-reductase inhibitor to mammal in need thereof. The combined preparation can be administered simultaneously, separately or sequentially.

Methods for the treatment of BPH or LUT with or without BPH, comprising administering a single dosage form containing a therapeutically effective amount of selective $\alpha_{1a}$ AR antagonist as disclosed herein, therapeutically effective amount of a MR antagonist and optionally included testosterone 5α-reductase inhibitor to a mammal in need thereof.

The suitability of alpha 1a adrenergic receptor antagonists in this invention can be determined using the assay methods, for example, those disclosed in *J. Auton. Pharmacol.* (1996), 16:21.

The suitability of muscarinic receptor antagonists in this invention can be determined using the assay methods, for example, those disclosed in *Life Sci.* (1999) 64:2351 and *J. Med. Chem.* (1999) 42:1999.

The pharmaceutical compositions as described herein can be administered together combined in a single dosage form or they can be administered separately, simultaneously or sequentially, each in its dosage form but as part of the same therapeutic treatment program or regimen. Separate administration of each compound, at different times and by different routes, will sometimes be recommended.

Other pharmaceutical component may also optionally be included as part of the combination for the treatment of BPH and LUTS associated with or without BPH.